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ENVIRONMENTAL PROTECTION AGENCY

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SCIENTIFIC ADVISORY PANEL

OPEN MEETING

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**OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361**

The hearing in the above-entitled matter, convened
pursuant to notice, at 8:40 a.m.

Thursday, June 25, 1987

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Room 1112
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EPA SERIES 361

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P R O C E E D I N G S

DR. KILGORE: I would like to call the meeting to order.

We have two additional reviewers today that I would like to introduce. On my immediate right is Dr. John Doull from the University of Kansas, Kansas City Medical Center. And on my immediate left Dr. Leon Burmeister, University of Idaho, College of Medicine.

I would like to welcome you two gentlemen.

I also would like to take a couple of moments and run around the room quickly and have the panel members introduce themselves. And I would also like to go to the audience and have the audience introduce themselves. So we will start with Dr. Jim Tiedje.

DR. TIEDJE: Jim Tiedje of Michigan State University.

DR. CLARKSON: Tom Clarkson of the University of Rochester.

DR. BERGMAN: Harold Bergman of the University of Wyoming.

DR. SWENBERG: Jim Swenberg, CIIT.

DR. KILGORE: And I'm Wendell Kilgore, University

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of California.

And on my immediate right --

DR. GRISHAM: Joe Grisham of the University of North Carolina.

DR. KILGORE: Thank you.

Now may we go to the audience and start over here, please?

(Whereupon, members of the audience identified themselves, as per attached sign-in sheet.)

DR. KILGORE: I turn the meeting over now to Steve Johnson who has some announcements to make.

MR. JOHNSON: I would like to welcome all the panel members and members of the public this morning.

A couple of brief announcements. First, if you have not signed in, please do sign in at the table in front of the room. Please sign in and put the appropriate information down.

Second, I would like to remind everybody that there is no smoking in this room.

And that's all of the administrative announcements that I have.

Thank you.

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DR. KILGORE: Our first item on the agenda this morning is consideration by the agency of scientific issues in connection with the Peer Review Classification of 2,4-D as a Class C Oncogen.

And Dr. Van Gemert is going to present the item for EPA.

DR. VAN GEMERT: Good morning. My name is Marcia Van Gemert, and I am a section head in the Toxicology Branch of EPA, and I will be presenting the deliberations of the Peer Review Committee on content 2,4 dichlorophenoxyacetic acid.

The issue before the panel this morning is whether the panel agrees with the Peer Review's classification of 2,4-D as an intern Category C Oncogen.

2,4-D has been used extensively for the past 40-years as a growth regulator and herbicide on broad leaf plants. The relevant toxicology studies examined by the Peer Review Committee included a mouse oncogenicity study, B6C3F1 mice, a rat chronic oncogenicity studies in Fischer 344 rats, within a population case control epidemiology study and farmworkers from the State of Kansas.

In the mouse study, the Peer Review Committee

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concluded that no tumors were seen at the highest dose testing of 45 milligrams per kilogram. But an MTD had not been reached in this study, and they recommended that the study be repeated using higher doses in order to achieve an MTD.

In the rat study, an increase in astrocytomas was seen at the high dose in male rats, at 45 milligrams per kilogram, which was merely significant using the Fischer's exact test where the P value of 0.054, but was highly significant using a Cochran-Armitage trend test.

The Peer Review Committee concluded that an MTD may not have been reached in male rats and recommended that a repeat oncogenicity study be done in rats, using higher doses and increased numbers of animals per group, and only brains would be examined for tumors.

Mr. Jerome Blondell of the Exposure Assessment Branch will discuss the epidemiology issues.

MR. BLONDELL: The National Cancer Institute study in Kansas focused on three types of cancer, soft tissue sarcoma, Hodgkin's Disease, and non-Hodgkin's lymphoma.

An initial analysis found significant associations between non-Hodgkin's lymphoma and six different groups of

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pesticides. There were no associations found for soft tissue sarcoma or Hodgkin's Disease.

More detailed analyses consistently pointed to chlorophenoxy herbicides as the most likely reason for the association with non-Hodgkin's lymphoma.

EPA requested four external reviews from individuals with expertise related to pesticide epidemiology. Each reviewer was provided not only the National Cancer Institute study, but other relevant studies, especially those done in Sweden. They examine the possible association between cancer and herbicide use.

Reviewers were asked to comment on the weight of evidence regarding the 2,4-D, non-Hodgkin's lymphoma association. Reviewers had conflicting views on the strength of support from other studies, as we do studies by Hardell which seemed to provide additional evidence of a chlorophenoxy herbicide non-Hodgkin's lymphoma association were characterized as having an important methodologic limitations even by the most favorable reviewer. This reviewer commented that the intense media attention of the time of the Swedish studies may have biased the respondents' reports of what pesticides they had used.

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The National Cancer Institute study did not have this problem. In their study, several different analyses found that reported herbicide exposure among users for 2,4-D was consistently associated with non-Hodgkin's lymphoma.

One of the most serious questions reviewers had for the National Cancer Institute study concerned the accuracy of the exposure data, especially for the half of the respondents that were next of kin. It seemed unlikely that they would be able to recall accurately what pesticides the deceased cancer subjects or controls had used some 10 to 30 years ago.

Based on the external review comments, our Peer Review Committee found that the data were inadequate to conclude that 2,4-D was the cause of excess risk of non-Hodgkin's lymphoma in farmers.

The National Cancer Institute is currently conducting two follow-up studies, one in Iowa and Minnesota, and one in Nebraska which we hope will clarify this situation.

DR. VAN GEMERT: Based on the weight of evidence, the Peer Review Committee concluded that there was only limited evidence of oncogenicity in male rats, and classified 2,4-D as an interim Category C oncogen. That is a possible human carcinogen with limited evidence of carcinogenicity in

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animals, based on the fact that 2,4-D produced tumors in only one sex of one species in a study where the MTD might have not been reached.

The epidemiology study in Kansas farmworkers did not provide a definitive link between 2,4-D and human oncogenists. The interim category was assigned pending receipt by EPA and evaluation two repeat oncogenicity studies in rats and mice and additional forthcoming epidemiology data.

The issue to be decided by the panel today is whether the panel agrees with the Peer Review Committee's classification of 2,4-D as an interim Category C oncogen.

Thank you.

DR. KILGORE: Thank you very much.

Any questions from the panel?

Dr. Swenberg.

DR. SWENBERG: I would like to clarify a couple of things here.

In the report, you had stated what my recommendations were, and they didn't come out quite right so I would like to clarify that.

Firstly, I considered the data equivocal, as you said. I did not consider the 15 milligram per kilogram animal

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data to be an increase. So it's only high dose.

And my recommendation was for two controls and two high dose run at the 45 milligrams per kilo, and I didn't say anything about increased number of animals.

DR. VAN GEMERT: Right. That was our recommendation, the Peer Review's recommendations.

DR. SWENBERG: Well, what came out in here was one high dose and two controls, larger numbers of animals and at higher doses. I just want to clarify that's not my recommendation.

DR. VAN GEMERT: Right.

DR. KILGORE: Any other comments?

Dr. Clarkson.

DR. CLARKSON: You mention some of the epidemiology studies, but you didn't mention all of them. For example, the study in Denmark with Lynge's study. Did you consider that?

MR. BLONDELL: Yes, that was one of the studies that we sent to all four of the reviewers was the study by Lynge.

DR. CLARKSON: And what weight did you give to that?

MR. BLONDELL: In general, the reviewers did not

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give too much weight to that, partly because it was a cohort study, the sample size was small, and there was some question as to whether enough follow-up time and a large enough sample had been present to show the kind of significant effect.

There was a slight excess of risk in that population of manufacturers in Denmark, but it was not statistically significant.

DR. CLARKSON: Didn't they have one after 10 years where they did find a significant excess?

The first report was that the whole group was looked at, and in the later, they had been exposed for a latent period of over 10 years.

MR. BLONDELL: For non-Hodgkin's lymphoma?

DR. CLARKSON: For the soft tissue.

MR. BLONDELL: Oh, for the soft tissue sarcoma. Yes, they did have a significant excess in the soft tissue sarcoma group.

DR. CLARKSON: Okay.

MR. BLONDELL: That's correct.

DR. KILGORE: Dr. Grisham. Oh, I'm sorry. Dr. Burmeister.

DR. BURMEISTER: Just one question. Point of

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information in terms of this being an interim classification.

First, the decision was made. Was there a feeling that the information from the Iowa/Minnesota study and the Nebraska study would be favorable at this time, or was that an expectation because those data are still being -- at least the Iowa and Minnesota are still being collected?

MR. BLONDELL: No, that was not an expectation. We understand that that will take at least another year before the development.

DR. BURMEISTER: I would say so.

DR. KILGORE: Dr. Grisham.

DR. GRISHAM: I would like to ask Dr. Van Gemert just to comment a little more extensively on the conclusion that the MTD wasn't reached in either of the groups, either mice or rats.

The question is about the MTD

DR. VAN GEMERT: The MTD in both the mouse and rat studies, we felt had not been reached.

In the mouse study, there were no life threatening - there was no life threatening toxicology seen. And in the subchronic study that they performed, this was also true. There was some toxicity seen in the kidneys, but it wasn't

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considered sufficient to cause a high dose of MTD.

And they did use a high dose of 90 milligrams per kilogram in the subchronic mouse study, and then backed off in the chronic study to 45 milligrams per kilogram. But, even at 90, we didn't feel they reached an MTD.

And in the rat subchronic study, the same thing occurred. There was some toxicity seen in the kidney, but it wasn't considered acceptable for an MTD. And the subchronic study the same.

DR. GRISHAM: And the liver hypertrophy, you don't increase it; in other words, you don't consider that?

DR. VAN GEMERT: No. The female rats in the chronic study appeared to have reached an MTD. There was some weight loss in the females. There was none in the males.

DR. KILGORE: Dr. Tiedje, do you have any comments?

(No response.)

DR. KILGORE: Any other comments?

DR. SWENBERG: Yes, I have a few more somewhat related to the MTD issue.

I guess in evaluating this whole packet, from the two generations reproduction study, 80 milligrams per kilo was too toxic. And I think maybe, based on the MTD document

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that this panel reviewed and just general considerations to try to titrate between 45 and 80 is going to be difficult. And I think your chance of running in to exceeding an MTD, if you changed doses, may create more problems than rerunning it at 45 and really learning whether this is a real effect or not.

DR. VAN GEMERT: We did see toxicity at 45, so we did see an MTD in the females. And in the two generation reproduction study, yes, I believe there was an MTD reached, and there was some toxicity seen. But it was the males that we took issue with, the male rat.

DR. SWENBERG: Well, but they also show several toxic end points. They might not be life threatening. But if 80 was life threatening and 45 wasn't, from the MTD document this panel reviewed, if you get within that kind of a factor, that should be acceptable. At least that was the way I understood that that document read and that we agreed with. And I think if you start trying to get something in between there, you may blow the whole thing. You may exceed the MTD and then you don't know what to do with the data.

I would like a clarification on something else though. There was mention in the documents, but we didn't

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have documentation on it, on bringing tumors induced by a related compound, 2,4-D-B, can you provide us with that information?

DR. VAN GEMERT: I didn't provide that information because I took a look at the review, and I wasn't satisfied with the review. I called the studies up and the studies -- not that the studies are inadequate, the studies appear to be adequate, but the review was inadequate, and I am having the study rereviewed by Dynamac right now.

I didn't agree with the review. I didn't see any increase in brain tumors.

DR. SWENBERG: What was the data? What were the numbers?

DR. VAN GEMERT: There was one in the control and three in the low dose. These were not astrocytomas. The reviewer had lumped all brain tumors together, and then called it brain tumors. And when I read his review, it said brain tumors only. So I went back to the study itself, and it was obvious that he had lumped all these things together.

DR. SWENBERG: So we should discount that base?

DR. VAN GEMERT: That's correct.

DR. SWENBERG: Thank you.

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DR. KILGORE: Dr. Doull.

DR. DOULL: In that regard, Jim, I wonder if the Blue 2 data wouldn't be relevant?

DR. SWENBERG: The problem with the Blue 2 data is it's Sprague Dawley's, and Sprague Dawley's are showing considerable variability in brain tumor incidents. But I'm not aware of Fischer rats showing that same degree of variability. That's the concern.

DR. DOULL: Yes. I do have one question, one concern.

In the epidemiology study concerns the fact that the farmers used 2,4-D over a long period of time, and there was some question about the kind of contaminants that may have been involved in 2,4-D over that period of time.

There is some data in here about the kind of dioxins that one sees in 2,4-D, not the bad ones, but all the other kinds.

In the Canadian review of this issue, they spent sometime talking about the nitrocyimine contamination. I wonder if you all have looked into that?

DR. VAN GEMERT: Yes, we did. In the formulated product that the workers would be exposed to, you have

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between .3 and 5 milligrams per liter of nitrocymine of nitrosodimethyamine, and that's considered to be a very low quantity.

DR. DOULL: The other thing. When I read through these documents, the Hazelton rat study and the mouse study, I could not find in there what these were actually done on. Were they done on a formulated product or on technical material?

DR. VAN GEMERT: Technical material. At least 97 percent, as I recall, 97 percent technical material.

DR. DOULL: As I recall, when this panel looked at 2,4,5-T, it turned out that if you look at pure 2,4,5-T, it's clean. But if you look at the formulated product with two or three dioxin in it, you have a problem.

I guess I'm wondering about the possibility here that if these studies really had looked at the product as the human population is exposed to it, whether the results might have been different?

DR. VAN GEMERT: You would certainly have a much more dilute product. And this is a far more concentrated situation. You would be giving a far greater quantity of 50 to 100 times more. You would have to use lower doses or you

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would be getting a liquid.

MR. BLONDELL: We do know, I might add, that the way the 2,4-D was made back in the fifties, as compared to the 1960s and seventies, that it was a much dirtier process in terms of the fact that there probably were more of a mixture with some kind of contaminant -- there would be more potential for contaminants to be present in the earlier years as compared with the way they process it now. That's our understanding.

DR. DOULL: Well, there is a lot of -- the Academy has looked at the Agent Orange problem, and there's a lot of information which says that the original Agent Orange was quite dirty and that, over the years, it was changed, which would involve both 2,4-D and 2,4,5-T.

DR. KILGORE: We thank you very much.

Jim.

DR. SWENBERG: Yes, still a few more.

You had a statement in your summary that range data on brain tumors wasn't available from the MTD. As I recall the Solleveld paper in 1983 gave the range of brain tumors as one of the tumors that was showing some variability. I think it was like zero to three.

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DR. VAN GEMERT: I recall that. It was zero to 1.7 percent, the study you are talking about. That was the one. It was brain tumors in general as far as I could understand from that paper. And then they discussed the fact that gliomas in brain tumors would account for 51 percent of the brain tumors seen in these studies. So they broke it out twice.

DR. SWENBERG: Do you have a copy of that article?

DR. VAN GEMERT: I think so.

DR. SWENBERG: We might be able to clarify that later in the day.

DR. VAN GEMERT: Okay.

DR. SWENBERG: The other question I had for you is, and this probably comes back -- no, it shouldn't.

Why are you recommending retesting in female rats?

DR. VAN GEMERT: That actually wasn't discussed. It should be retested in male rats definitely, but we hadn't come to the conclusion that females should be tested. That was not a recommendation.

DR. SWENBERG: It was a recommendation in -- it was set with tables of contents, stapled to it. That was one of the recommendations.

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DR. KILGORE: Any additional comments at the moment from the panel?

If not, we will go on to the public comments, and I understand that Mr. Robert Morgan, Chairman, Technical Committee, Industry Task Force on 2,4-D Research Data has requested time to speak and appear with his associates.

Mr. Morgan.

MR. MORGAN: Thank you. Actually I will be present at the table with the speakers.

DR. KILGORE: Okay. Would you introduce your associates, please?

MR. MORGAN: Yes.

Actually Dr. David Serrone will be making our comments or initiating our comments.

DR. SERRONE: Good morning. My name is David Serrone. I worked with the Industry Task Force on 2,4-D research data for seven years. With me this morning is Mr. Robert Morgan, Dr. David Eisenbrandt, Dr. Bert Koestner and Dr. Greg Bond.

I will review epidemiology and our rationale dose selection for the chronic studies. Dr. Koestner will address the biological aspects of the astrocytomas.

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As for the epidemiology, much attention has been focused on the NCI study, which some people have interpreted as suggesting an association between 2,4-D and non-Hodgkin's lymphoma. Three of the four scientists who reviewed the study on behalf of EPA, concluded that it did not establish an association between 2,4-D and NHL. The conclusions of the fourth was incongruent even with those of the authors, who have been widely quoted as saying this study is not a sufficient basis for regulatory action.

Of course, a single observational epidemiology study cannot establish a causal association between 2,4-D and any disease. Consistency of findings from multiple studies of various designs conducted by different investigators is required. A review of the literature shows a failure to meet this consistency test. In fact, recent studies from Western Washington State, New Zealand and an NCI study, one of those cited by EPA as pending from Iowa and Minnesota are very strong studies and suggest no association between 2,4-D and non-Hodgkin's lymphoma.

Should you have questions concerning epidemiology, Dr. Bond would be happy to respond to them.

I would like to review with you our scientific

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rationale for the dosages selected for the chronic studies. The agency is apparently recommending that the sponsor repeat the chronic two-year studies, because of the impression that higher doses of 2,4-D could have been tested. The real issue is, were the levels high enough to evaluate the oncogenic potential of 2,4-D? We believe they were.

We initially had pharmacokinetics data. These studies were carried in both rats and mice using both oral and intravenous routes of administration. Results were similar in both rats and mice. The kidney is the primary route of elimination of 2,4-D, and it is excreted essentially unchanged. And kinetics become non-linear above 50 milligrams per kilogram.

2,4-D is a substrate for the organic acid transport system in the kidney. Saturation in this transport system would explain the decreased urinary excretion of 2,4-D, expressed as a fraction of the dose, observed in animals given more than 50 milligrams per kilogram. The disproportionately large increase in plasma 2,4-D concentrations following doses of 100 and 150 milligrams per kilogram provided additional evidence that the elimination of 2,4-D was saturated in animals given more than 50 milligrams per

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kilogram. As a consequence, the dose response curve for 2,4-D would be expected to increase disproportionately at dose levels above 50 milligrams per kilogram.

There were three subchronic toxicity studies done in rats and one, 13-week study done in mice. A decrease in the rate of body weight gain occurred in both male and female rats at 100 and 150 milligrams per kilogram per day. The kidney was identified as a primary target organ and effects were observed on kidney weight and morphology.

In the mouse 13-week study, microscopic alterations in renal proximal convoluted tubules were observed in both males and females at all dose levels. The dosage levels selected for the chronic studies were determined from this data base, with the highest level predicted to adequately evaluate the oncogenic potential.

Dose level selection was based on the subchronic studies and the pharmacokinetic studies which indicated non-linear kinetics and significant toxicity at levels above 50 milligrams per kilogram per day.

This data has been prepared for publication and it has been accepted in Fundamental and Applied Toxicology.

In the combined chronic toxicity and oncogenicity

study in rats, decrease in body weights, decrease in food consumption and increased kidney weights were seen at the 45 milligram per kilogram per day dose in males and females.

In the oncogenicity study in mice, there was demonstrated an increase in kidney weights in mid- and high-dose females and in high-dose males, an increase in the cytoplasmic homogeneity of renal tubular epithelium due to reduction in cytoplasmic vacuoles was observed in mid- and high-dose males.

It is the opinion of the task force that the dose levels chosen for these chronic studies were appropriate.

As to the statistically identified difference in brain astrocytomas, a peerwise statistical test was not significant at $p = .05$ level. A trend test was positive. To find one statistical comparison such as this in examining a study of this size is not surprising. Government statisticians at the NTP and FDA recently have cited the need to be aware of false positive issue, and not to regard every statistically significant effect automatically as a biologically meaningful result.

Statistical analysis alone do not identify carcinogens. Rather, they are tools to identify findings for appropriate biological evaluation. We have turned to Dr. Koestner

for a biological analysis of this finding.

DR. KOESTNER: In my report, I presented 11 biological criteria to be used to separate spontaneous neurogenic tumors from those produced by a neurocarcinogen. Now, the 26 neurocarcinogens I am aware of from literature and from my own work comply to several or most of these criteria, but 2,4-D did not comply to any of these criteria. The only incriminatory feature is the tumor distribution with the highest rate occurring in the high dose group.

In overall, the glioma incidence in the male and female rats is almost as expected, and I will spend a little time to explain that.

There are obvious issues which need clarification. I want to take particular issue with the idea of the widely emphasized distinction between two unit lifetime glioma incidences in F-344 rats. The Solleveld paper, in which this comparison was made, refers to NPT two-year control data from 2,320 male and 2,370 female rats versus noncontrolled data from 525 males and 525 female rats. The table which you have in my handout, the first page shows this.

You will see in that table that in the male, the astrocytoma, oligodendroglioma, and glioma unspecified

together make about 19, which is a .8 or close to 1 percent incidence. This is the so-called two-year study, but it is up to 116 weeks. The 15 gliomas in the lifetime study make up a 2.9 percent incidence, and in the female, it is .7 and 1.8.

I would like for you to take a look at the last page of the handout, which shows the survival curve of these animals in the so-called lifetime study. Now, you can see at 116 weeks, the animals start to die fast. At 120 weeks, only 50 percent of the animals are still alive, and then they really die fast because at 140 weeks, less than 10 percent are alive.

I think this is an important issue. So if we analyze these two years versus lifetime analysis, we must realize that the data in the two-year study is 116 weeks. This is the comparison which one must make of the incidence.

My contention is that the idea that the majority of the gliomas in the F-344 rats develop in the few weeks after 116 weeks must be a misconception. It is more likely that the tiny tumors are missed in the two-year study upon microscopic examination of only three brain sections and detected several weeks or months later when they have doubled or tripled in size. In previous widely publicized studies, that is, the

aspartame study and the blue-2 study, there were similar glioma distribution problems as in the 2,4-D study existed, and additional brain sections were requested, and these additional brain sections also revealed additional gliomas, although the sections came from the same blocks from which the first sections came and were just microtumors located a little deeper in the block, because they were that small.

Now, in contradistinction, in the 2,4-D study, you are not dealing with multiple sections from three blocks. We are dealing with sections from seven brain slices. Now, these slices were sometimes familiar of the brain which are normally never represented and take coronal sections, such as the olfactory bulb.

Two of the gliomas, both about 1 to 2 millimeters in diameter, demonstrated in the olfactory bulb, would not have been recognized in ordinary studies, because that would not have been cut.

It is my contention that this most thorough study detected gliomas which would not have been discovered in a routine study at two years, but only after they have grown larger and perhaps have become grossly visible. It is therefore justified to compare the incidence in the 2,4-D study

with that of the so-called lifetime incidence. Compared to Solleveld's data, 2.5 percent in the male and 1.8 in the female, in the 2,4-D study it is 2.6 in the male and 1.6 in the female, and this is if we take all the tumors of all the animals, this is about half the animals which Solleveld had, and say nothing has been done to that, but a number of tumors would be expected. If we do this, then I think they are just about right as we would have expected it.

Now, if you look at the table, which is the second from the last page, it shows the distribution of the astrocytomas in the Solleveld study, the one with the large letters. Here are the five control groups. They have a 4.5, 1.2, 5.9, 0, and 1.7 incidence, so you have a very similar spread than we have with anything else, and I cannot see why it should be different in the Fischer rat.

There is something different in the Fischer rat. I think perhaps in the Fischer rat, either the initiation is later of spontaneous tumors, or the progression is slower, because this is the only explanation, because if we use the Fischer rat with neurocarcinogens like ENU or MNU, they are about equally susceptible to the Sprague Dawley rat.

Now, I would like to impress upon you the spread of

tumors in animals, and perhaps if you go one page further, in front, there is one where I said selected comparison of tumor incidence within matched control and treatment groups, and I have written in mice, and this is from the Blue-2 study.

I just looked to the Blue study in mice and I selected the 2,4,6 malignant tumors which were zero in the high dose group, and then I looked in the control group, and it had between 5 and 12 percent. So I don't want to say that Blue-2 protected these animals from developing tumors; I just want to show you that we should expect this type of a spread. This is not unusual and statistics cannot answer in this case our problem.

Now, there is one more point I would like to make in regard to the review of the EPA group. On the fourth page of the EPA group, numerically, compare the incidence of the 2,4-D only with the astrocytomas mentioned in the NTP study. I don't think this is acceptable. The table on your first page shows there are astrocytomas, oligodendrogliomas, and gliomas unspecified. They might as well be astrocytomas which were too anaplastic to recognize or they were mixed tumors.

Now, we lump all these tumors and gliomas together, because all types of these gliomas occur spontaneously and all

are produced with no neurocarcinogens. In our experience, they start out as monomorphic oligodendrogliomas or astrocytomas and become more mixed and anaplastic as they increase in size.

DR. KILGORE: Any questions from the panel?

DR. GRISHAM: I was interested in your conclusion, Dr. Koestner, that you, from the biologic standpoint, concluded that the astrocytomas in the treated animals were more likely spontaneous because you can find evidence of precursor lesions.

DR. KOESTNER: This was only 1 of the 11 criteria.

DR. GRISHAM: The question, though, was -- I guess I sort of fundamentally believe that spontaneous mutations or spontaneous -- the developing neoplasms have the same fundamental mechanism by which they arise whether we do it with a chemical or radiation or whether it's "spontaneous."

I wondered what your evidence was that in induced lesions, there was always the spectrum of precursor lesions.

DR. KOESTNER: I think for this particular purpose, it is one of the weaker criteria. I think obviously, there were no precursor lesions before the time, but I think that the whole experiment was not designed to look for that. Dr.

Swenberg and I have done studies where we killed these animals on a weekly basis, so this is only when you can really do it well, but I think it would have helped if one would have seen this.

I think the major thing is that the overall incidence was not increased by the substance, if we take the basis which I have presented. Secondly, there was not a shift to younger age. This is usually the case actually with the weakest neurocarcinogens. The animals have died by 15 months and by 12 months was sometimes the average.

There are other things. There was no tumor in any other organ which mostly happened. There were no multiple tumors. There was no tumors of the peripheral nervous system.

So a lot of these criteria, I think have applied, not all of them in every case, but here, not a single one.

DR. EISENBRANDT: If I may make one comment. I am Dr. David Eisenbrandt. I am a pathologist.

In regards to that question, I have reviewed slides on studies with acrylonitrile and acrylamide. In those studies where there is a significant increase in tumors, they tend to occur at an earlier age. As you review those slides, you will see a spectrum of lesions. In fact, in the acrylonitrile

studies, a lot of the original diagnoses were gliosis, where they weren't even convinced those were a real tumor, but that is the kind of preneoplastic prolific type of change. I think, in retrospect, most people now lump all of those together in one category, but I think that is the kind of preneoplastic change that would be looked for in a true response.

DR. KILGORE: John?

DR. DOULL: I have a question for Dr. Koestner.

I am not sure I understood, Bert, what you were saying about the way in which the sections were done in the rat study. You were saying that they did not go back to the blocks and get additional --

DR. KOESTNER: The Hazelton study, they saw there is some difference of tumors, and they just went back and embedded the rest of the brain, so they had a total of seven blocks, which means that the sections here are received from seven different areas of the brain, while in the aspartame study and the Blue-2 study, they were requested by the FDA to present more sections, and then they cut just deeper in the block, and indeed, they did find lesions in these cases, because the tumors are so small that they just go a few

millimeters deeper in, you may find another lesion.

I just think in the 344 rat, we have two choices. Either we request that more blocks are cut at the two-year study, or we just let them live at least 120 weeks. By that time, perhaps someone would find them.

So there is something different either with the progression, but I think the tumor may be very close to what we see in the Sprague Dawley rat.

DR. DOULL: I guess I would ask Jim, does NTP have a procedure for that if they find liver tumors or something, do they go back, then, and slice more? How do they do all that?

DR. SWENBERG: No, they have a set number of sections they take plus gross lesions. You can end up with a few additional sections if there is a grossly visible tumor, but they don't go back and embed the whole liver.

DR. KOESTNER: That is always a chance one misses.

DR. SWENBERG: Bert, I have some questions I would like to discuss with you.

Firstly, on these 11 criteria, I would like you to think back to the paper we published on ethylnitrosourea and 1 milligram per kilogram data. Tell me how that data compares.

DR. KOESTNER: I think was a very marginal dose, as I recall, and we had a tremendous number of animals developing tumors of other organs, which we considered occurred normally, and I don't know whether we can even compare this.

DR. SWENBERG: I think it is actually quite a nice comparison, because we had a 13 percent incidence of tumors of the nervous system. We had a multiplicity of one tumor per animal. We had no change in latency in that dose group.

I think the reason I am as cautious on this data as I am, I firmly believe it is equivocal. I don't believe that it is positive. But I also don't believe that it is just plain negative, as the statements have said. We are following into a situation of here, the Canadian report said it is not adequate to call it positive, but they didn't call it negative.

DR. KOESTNER: Let me compare it to another thing, to the ethylene oxide, where it is a very controversial tumor incidence. Six animals died from brain tumors prematurely, 10 to 20 weeks before the thing was ended in that paper which was presented in Sussex.

DR. SWENBERG: I am not sure about that. I had ethylene oxide written down as my other comment. There were two studies on ethylene oxide. One was by NIOSH, one was at

Bushey Run. They came up again with a similar incidence to what this study has, but it was repeatable. That was what made it convincing and made one believe it was real. They again had one tumor per animal, and they didn't have the early stages.

So I think when we get into this kind of a weak effect, we have to be very careful in pulling in all those 11 criteria.

DR. KOESTNER: But if you look at the study of ethylene oxide, they say clearly that the so-called intermediate death, which they call it intermediate deaths, which were all from about the 90th week to 104, and the study was terminated at 116.

Now, in that intermediate death, they all occurred in the high and the second of the highest doses, and it said 66 animals they believe have died, the primary cause of death was brain tumors.

DR. SWENBERG: No, wait. I think the primary cause of death was Fischer rat leukemia for most of those, and the brain tumors were incidental findings.

DR. KOESTNER: But that is what Dr. Garmon reported.

DR. SWENBERG: Yes, I know. I think we have a

slight difference of opinion on that interpretation.

DR. EISENBRANDT: It was considered positive in both sexes, though, wasn't it?

DR. SWENBERG: That's right.

DR. EISENBRANDT: As opposed to we only had an effect at that single high dose.

DR. SWENBERG: No, I think it was only in one sex.

DR. KOESTNER: In the high and then the second high dose, there was this death of animals prematurely. There was a female increase in tumors, as well. We have several theories which somehow apply, but nothing of that really happens in the 2,4-D.

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DR. SWENBERG: The issue on comparing with the Sollevelld data and the number of sections per brain and the tumors in the olfactory bulb is an interesting area to discuss.

I think it is very difficult. We really cannot compare the data of this study with seven sections per brain with the NTP two-year data base. You know, they are just apples and oranges because of the numbers of sections. And two of the tumors were present in the olfactory bulb. That is true, and that is not a normally examined portion, and they were microscopic in size.

DR. KOESTNER: You take these away, you have a completely different story.

DR. SWENBERG: On the other hand, the life span study does represent a 25 percent increase in life span. I have spent a lot of time reviewing that study on tissues other than just the brain, and you will find that many tissues increase their tumor incident by a factor of 2 to 31. The parathyroid gland increases its spontaneous tumor rate by a factor of 31-fold.

I am not sure, though, that it is an adequate comparison to look, say, well, seven sections in this study is equivalent to lifetime in that study.

DR. KOESTNER: At least tumors were detected which we have assumed that we detected tumors which we wouldn't have if we had only cut three sections.

DR. SWENBERG: I guess I would ask for your professional opinion, then. Do you believe that this study demonstrates a negative effect in the brain?

DR. KOESTNER: I think so. I think this would not really --

DR. SWENBERG: What would your criteria for that be?

DR. KOESTNER: The criteria would be, first of all,

that the overall tumor incidence, if I make this comparison --

DR. SWENBERG: It's double, it's twice as high in the 2,4-D, even with your way of comparing it.

DR. KOESTNER: No, no. I say that the overall tumor incidence in that group of rats, if we just consider that anything should have been done, because if I take the table of Solleveld, I could easily make a -- you could say, well, why don't you assign to the 5.9, it's a 6 percent incidence to the high dose group, and so you can easily get a discrepancy here.

Now, I would say that --

DR. SWENBERG: Well, this is 6 percent versus 10 percent. I mean you are taking the very worst possible case from the Solleveld data versus this data.

DR. KOESTNER: Yes, but I think --

DR. SWENBERG: And this one is still higher, and you think that that proves a negative?

DR. KOESTNER: The percent is very impressive, but it takes just one tumor away, and so the percentage immediately goes down about a half a percent. I understand. I sense a discrepancy here, and I understand the problem.

DR. SWENBERG: You don't think the data is equivocal

rather than positive or negative?

DR. KOESTNER: Well, I understand you are saying it is equivocal. I had the impression that since none of this criteria -- there was really no increase in the whole tumor load of that group of animals. If we lumped these animals together, all the animals, and say it is a 2.6 instead of 2.9, there was not really an overall tumor increase, which all other carcinogens really do.

DR. CLARKSON: Mr. Chairman, may I ask a question about humans now we have finished with the rats?

(Laughter.)

DR. KILGORE: I don't know whether we are finished with the rats yet or not. Are there any additional questions about the rats?

(No response.)

DR. KILGORE: Okay. Dr. Clarkson, go ahead.

DR. CLARKSON: You opened your presentation with a discussion, a brief discussion of the epidemiology, and you said a Dr. Bond --

DR. BOND: Yes.

DR. CLARKSON: There are so many epidemiologicals listed here, but it is difficult for my pea-brain mind to

remember everything that is wrong with every one of them. There was what I thought an excellent review by the Canadian group. I don't know whether you saw this or not.

DR. BOND: Yes, I have seen it.

DR. CLARKSON: Well, I thought it was pretty good anyway. It helped me to sort of look at these various studies and try to come to some conclusions about it. First of all, they grouped them according to the cohort study and case control.

In the cohort studies, there were several -- six they have listed here -- and only one was positive, and it was regard to soft tissue sarcomas in the Denmark study. These, of course, are not with regard just to 2,4-D, as you know. They are either phenoxy herbicides, and there is always a possibility already of contaminant.

At least with regard to the Canadian review, the ones that were negative were negative for good reasons, and as I read it, rather difficult, as we have just heard with the rat studies, in the case of a weak carcinogen, to say that there is some evidence against a biological effect.

They lack power, they lack a long enough follow-up period, exposure was so uncertain in many cases that they

were probably diluted by people who were not exposed or at a low exposure.

So when I read this Canadian review, anyway, of the cohort studies, I was left with the impression that there may be something here, that these negative studies were not really negative and that there was a positive study.

Now, here again, we are talking not about 2,4-D itself, but either about phenoxy herbicides as a group, and of course, with the problem of unknown or suspected contaminants.

What is your opinion about this, do you agree with this point of view, or my interpretation?

DR. BOND: I think there is a major misunderstanding about the Lynge study, the Danish study. That study was a massive group of chemical workers who manufactured not only phenoxy herbicides, but also manufactured other chemicals. I think there may have been some dyes that were produced at that facility, as well.

In fact, the authors did a fairly reasonable job of trying to sort out who would have been potentially exposed to chlorophenoxies, who had manufactured chlorophenoxies and who had manufactured the other chemicals. Unfortunately, I

think they misinterpreted their own data in that the soft tissue sarcomas that were observed in this study, were not in the chlorophenoxy herbicide production manufacturers, they were in the other groups.

Additionally, the non-Hodgkin's lymphoma cases in the study were not in the chlorophenoxy. For that reason, they concluded that there was no relationship between chlorophenoxy production and non-Hodgkin's lymphoma, but they didn't make the same conclusion about the soft tissue sarcomas, and that somewhat puzzles me.

When they separated the groups out, if you look at the chlorophenoxy group, there wasn't an excess of soft tissue sarcoma in that group.

I agree with you that the power of cohort studies is quite low relative to the case control studies. However, I think we often overlook a very important feature, and that is, the cohort studies have focused on the populations that were considered to have the greatest exposures to these compounds, people that were professional applicators, who had manufactured the compounds, and if you look at the detailed analysis of the cohort studies, like we have done here, it turns out that on the average, the subjects in the cohort

studies were exposed for years to these compounds, as opposed to the case control studies where the reported exposures in the case control studies have at most been a few years, but on the average have been measured in a couple of months of exposure.

Not only that, but the case control studies include a myriad of persons exposed in a variety of different contacts, certainly not the same kinds of exposures that would have occurred in the manufacture or application of the compounds.

I think for that reason, we really expect the cohort studies to show a much stronger effect, if there is an effect, than the case control studies, and we certainly don't see that, but I grant you that there is somewhat lower power with the cohort studies. But then again, as I mentioned, we expect to see a stronger effect in those studies.

DR. BURMEISTER: My reaction to that statement is that basically I agree, but the power is low, and there is a little bit of contradiction there. Of course, there is in all these studies. That is why they are so hard to interpret, in the sense that you expect more from the cohort studies. But if power is poor, then that is basically a discrepancy. So it is hard to make the judgments. One statement that I

might just put out relative to this discussion, sort of for discussion purposes only.

It was mentioned earlier today that all so-called statistically significant differences are meaningful and should be interpreted that way, and I would be in agreement with that.

Now, on the other hand, some of these results that are considered negative because they don't achieve statistical significance because perhaps of poor power, may be in the realm of studies that should not be considered negative because of the power.

What is your reaction? I am just wondering what your opinion is on that.

DR. BOND: Well, what we have done in our review is we attempted to pool the various cohort studies, and there is a lot of controversy about when you can pool and when you can't pool, and it was a difficult decision going through, really, as to how to pool the data.

DR. BURMEISTER: What was your justification for pooling just for the record?

DR. BOND: They were, first of all, similar studies in that they were cohort studies, they were cohort studies

of manufacturers and applicators. We did separate out -- and I think this is a very important point -- separate out the manufacturers of chlorophenols who would have been exposed to the dioxin contaminates at a much different level than, let's say, the cohort studies of the phenoxy herbicide manufacturers per se, the manufacturers of the phenoxy herbicides per se.

They had similar observation periods. They were all at least 20 years-plus latency. On that basis, we pooled, and if you do pool, it is quite remarkable. There is actually quite a substantial deficit of non-Hodgkin's lymphoma in the studies, not enough that we can say that there is -- we can't rule out any excess risk, but I think we can rule out the kinds of risks that have been reported from the case control studies.

DR. BURMEISTER: In the pooling operation, did you give the various studies equal weights, or did you do a weighted pooling?

DR. BOND: Well, they were given weights based upon the expected number of deaths from each study, so that the larger studies contribute more information than do the smaller studies.

DR. BURMEISTER: I didn't detect that from what was

written, but it was a weighted pooling, then.

DR. BOND: It was just weighted based on the -- what we simply did was add up the observed and expected numbers of deaths for total cancer, soft tissue sarcoma and non-Hodgkin's lymphoma, and for total cancer we can almost rule out any excess risk. In fact, there is a substantial deficit in the cohort studies of total cancer, which would indicate to me that at least 2,4-D is not a major public health problem.

DR. BURMEISTER: You mean all cancers combined?

DR. BOND: Yes, all cancers.

DR. BURMEISTER: Particularly in the farming literature, a lot of that is consistent with what you are saying.

DR. DOULL: I need to ask, Tom, if that is the answer to your question, your evaluation of whether this data is equivocal or negative. I thought I just heard you say negative. Is that what you said?

DR. BOND: What I said was I think by looking at the cohort studies together, we can rule out -- we can certainly rule out the kinds of risks that were reported from the case control studies, a twofold risk of non-Hodgkin's lymphoma.

Getting down into whether or not you can rule out

a 50 percent increase or smaller, the data just aren't there to rule out smaller risks. But certainly the point estimates of risks, the best estimate from the cohort studies is that there is not an increase in non-Hodgkin's lymphoma, that there is not an increase in soft tissue sarcoma in these populations, but it is just that the confidence limits about that point estimate of risk still do not exclude risks above $1\frac{1}{2}$.

DR. DOULL: I guess what I am saying is when Dr. Clarkson was asking you about that, he quoted the Canadian conclusion which is that 2,4-D cannot be exonerated on the basis either of the cohort or the case control study. I thought I heard you say something different.

DR. BOND: The exoneration doesn't take into account the strength of the association. No study can exonerate -- we will never have enough studies to exonerate 2,4-D.

What I think you can say is that you can exonerate certain strength of association, and certainly risks above twofold, I think we can say with confidence from the cohort studies, 2,4-D does not increase the risk of non-Hodgkin's lymphoma certainly more than $1\frac{1}{2}$ to twofold, and our best estimate is that it doesn't increase the risk at all.

DR. CLARKSON: Can I ask you about that point? When

you say you can exclude risks, relative risk like the factor of 2 from the case control, there is still this problem of the dilution effect, that you don't know your exposure that well, and so I have some problems with that. In these cohort studies, you know, the measure of exposure is very poor.

DR. BOND: Yes, but -- well, I don't think it is any poorer than the case control studies where all of the exposure information is coming from recall. Here, in the cohort studies, at least the exposure is documented, either work history records. We know that these people were working in this job, were being paid for doing some work that would have involved exposure to these compounds.

I agree with you that the precise kinds of estimates that the toxicologists are able to come up with for dosing are rarely available in epidemiology. One of the studies that we did review, however, is a study that we did at Dow, of our own employees, where we had industrial hygiene monitoring data to estimate exposures.

Now, to my knowledge, that is the only study out there that has tried to look at level of exposure, a quantitative estimate of exposure.

DR. CLARKSON: Oh, I see the problem, that when you

do that, you are limited to a small number of people because of the difficulty of making these measurements. It is an endless problem, as you say, to really answer this.

Could I proceed just to ask you a bit more about the case control, now that we have talked about the cohort? Again, I am referring back to this Canadian review. It was said, I think by your group, that, for example, the Swedish study suffered from this bias in recall, because they were cases with biased recall, and, as it often is in Sweden, in the newspapers, and so on, at the time.

But they had a reply to that, and in your comments, you didn't deal with their reply, that I recall, that they also did a study on colon cancer, and their point was that if there was bias in recall, they should have seen a similar effect with colon cancer, similar association with herbicides.

DR. BOND: That is addressed in our review.

DR. CLARKSON: Oh, I am sorry. But it wasn't addressed this morning, okay.

DR. BOND: In the review, it is addressed. The colon cancer study was conducted -- and this is probably the first time I have ever been aware that someone has done a study trying to show no association, so that they could prove

that their methods in earlier studies were appropriate.

The study was done about two to four years after the initial studies had been done. I don't think the debate in Sweden persisted at the level of intensity on the phenoxies as it did at the time of the earlier studies. It is impossible to know, I guess is what I saying, whether or not all of the aspects of the studies that were done on soft tissue sarcoma and non-Hodgkin's lymphoma by the Swedes were replicated in the study of colon cancer.

I think probably the strongest argument that there may be something wrong with the Swedish findings is when we look at the data from the rest of the world, and we look at the work of Wiklund and Holm within Sweden. They have done an analysis of cancer rates among Swedish forestry and agriculture workers, where they subcited those that had reported work in forestry or agriculture in the census according to their level of potential exposure to phenoxy herbicides, and then computed the cancer rates looking at soft tissue sarcoma and non-Hodgkin's lymphoma.

They can rule out the kinds of risks that Hardell was observing in his study. In fact, they can rule out risks above 1½ for soft tissue sarcoma and non-Hodgkin's lymphoma.

DR. CLARKSON: Even with their poor identification of exposures?

DR. BOND: Even with the poor -- even if you assume the worst case of dilution in those studies. In fact, I think the Canadian report review speaks to that very well, that, in fact, here is where the final answer in the Swedish studies may come, is that Wiklund and Holm are actually going back and they are doing a case control study based upon their work. I think it should finally answer some of the serious questions that people have raised about the Swedish work.

DR. KILGORE: Excuse me a minute, Tom. Could I interrupt, it is time for us to take a break here. Can we take a break and reconvene at 10 minutes after 10:00.

(Brief recess taken.)

DR. KILGORE: I would like to go back to Dr. Clarkson now, and I think continue his questioning. We are finished with the rats and mice, I think.

DR. CLARKSON: No, we are not finished.

DR. KILGORE: I will give you some more time.

DR. CLARKSON: I just have a few more questions about the case control studies. I am looking at this Canadian document. We were talking about the problems with the Swedish

studies. And then it goes on -- which I think you mentioned, or your colleagues mentioned this morning, about other studies which were negative. One of them was the New Zealand study.

However, the Canadian review of the New Zealand study says, concludes these studies clearly do not demonstrate the absence of risk. There is a small, although not significant elevation of risk for both diseases and the confidence intervals would not exclude a relative risk of 2 or more depending on the case series.

I am coming back to I guess what we were talking about, the cohorts in a sense, that we have some criticisms of the positive study, that is, the Swedish one, because of the problems of recall bias. But on the other hand, again, as I read this Canadian thing, they are giving reasons why the negative case controls are negative, and it is the same kind of story, as I read through this.

I, therefore, have difficulty giving much weight to, shall we say, the absence of a finding of a New Zealand, the power of it, or the fact that it may have been diluted due to problems of exposure, and so forth, and the fact that they couldn't exclude a relative risk of 2 or 3.

Therefore, to me, this New Zealand study does not

contradict anything.

DR. BOND: I would agree with you that the single study is probably not persuasive, but I think if we -- could I maybe use the slides?

DR. KILGORE: Sure.

DR. CLARKSON: Mr. Chairman, I don't have a slide in my pocket. This is not fair.

(Laughter.)

DR. KILGORE: We will give you about 10 minutes to find one.

DR. BOND: I notice you did come prepared with the Canadian review, though. You have me at that disadvantage.

(Laughter.)

(Slides shown.)

DR. BOND: I won't say there is a slight bias in these studies, but there is a slight bias in these slides.

What we have done here is plotted the individual probability densities for the odds ratios from the five case control studies that related to phenoxy herbicide use to non-Hodgkin's lymphoma incidence.

In the five studies are the study done by Hardell, one of the original studies that link -- the original study

that linked non-Hodgkin's lymphoma with phenoxy herbicide use. This study by Sheila Horazam. The three most recent studies by Pearce, Cantor and Woods. If you look, the odds ratio is a measure of the association between non-Hodgkin's lymphoma and phenoxy herbicide use and baseline of 1 meaning no association.

You can see the discrepancy between the studies, with Hardell indicating 6-fold and above risks, the Hoar study indicating about a 2.2-fold risk, if I am not mistaken. The other studies centered really about unity, indicating no association.

We took and pooled the data or averaged the probability density ratios from the studies excluding the Hardell study. I did it in the report including and excluding the Hardell study, but based on the methodologic problems associated with the Hardell study, we did do it without the Hardell study, and I would like to show the next slide, which is the average, the net probability density for the odds ratios.

If you look at that, it indicates overall an odds ratio of 1.27, a 1.3-fold risk, with confidence limits of 0.8 to 3.31. So it is not indicating a very strong association at all. The point I want to make is that the Pearce study is

only one of the studies. There are many others, including the study by Cantor and the study by Woods, that I think need to be taken into account when you review the literature.

When we do that, and pool the data, even from the positive Hoar study, the association comes nowhere near being statistically significant, and it is a much more modest indication of risk.

Could I have next slide. We have done the same thing with the soft tissue sarcoma studies. The Hardell and Eriksson studies are to the right. Those are both Swedish studies. Hardell was involved in both. They are both suspected of having the same methodological problems, to the left of that, indicating really no association with soft tissue sarcoma; the studies of Smith from New Zealand, Hoar and Woods.

If we do the same thing, pool, look at the net probability density for the odds ratios from the three studies, excluding the Hardell studies, they indicate overall a point estimate of risk of 0.93, no association and nowhere near statistical significance. I mean the confidence limits come nowhere near statistical significance.

I think this is the kind of analysis that needs to

be done of these studies. Individually, the studies are probably not that persuasive, but as a total package, they are starting to paint a picture of really not much going on with either soft tissue sarcoma or non-Hodgkin's lymphoma.

DR. CLARKSON: So that these studies taken as a whole, could eliminate an odds ratio there of 2.2?

DR. BOND: That is an average of the studies. It is not pooling the studies; it's an average. It is assuming that each of the studies represents the same underlying population at risk, which I grant you is an assumption.

DR. CLARKSON: You mentioned the Wood study, which again didn't find any statistically significance.

DR. BOND: The point estimate of risk was well below 1. The best estimate was that there was no association at all.

DR. CLARKSON: The Canadians comment about this, they say that this seems to be a carefully conducted study and although overall no increased risk was found with phenoxy herbicide exposure, the subgroups where increased risk was demonstrated are compatible with a true biological effect. You don't agree with that?

DR. BOND: One of many of the analyses that was done

in that study, that was based, not on reported phenoxy herbicide use, but instead was based on a judgment of phenoxy herbicide use on the author's part based on the job title. He indicated an association in one small subset, but if you look at the overall, it did not indicate an association with 2,4-D, and analyses by duration and latency of exposure to 2,4-D revealed no association.

I think the Wood study is pretty emphatic on that point if you look at the abstract and the conclusions. The study was not capable -- or did not show, not that it wasn't capable -- it did not show an association with 2,4-D, any measure of 2,4-D exposure and non-Hodgkin's lymphoma or soft tissue sarcoma.

DR. CLARKSON: I guess none of them can specifically implicate 2,4-D, right?

DR. BOND: I think epidemiology studies are capable of implicating 2,4-D. The limitation that the Hoar study has, of course, is that they didn't ask about specifically duration and intensity of 2,4-D. They asked about herbicides in general. That is a limitation of a number of the studies, that, in fact, they lumped the phenoxies as a class, or considered herbicides in general, rather than looking at specific

types of herbicides.

DR. KILGORE: Dr. Burmeister?

DR. BURMEISTER: Just a reaction. It would be very difficult to find people that were exposed to only 2,4-D, so I am not sure that the case control studies or other cohort studies, et cetera, could really identify only exposure to 2,4-D or any other pesticide contaminant. There is always going to be a long-time exposure, or almost always.

DR. BOND: I don't think you need to have a purified exposure to demonstrate an association. It may be that 2,4-D use is always completely confounded with some other chemical. I don't know whether that is true or not, but hypothetically or theoretically, even if there is mixed exposures, you can tease out a single chemical. I don't think any of the studies has done that, however.

DR. DOULL: I might just comment that there are a group who are exposed almost exclusively to 2,4-D, and that is the highway weed sprayer group, and there are some data, in Kansas, for example, Fred Holmes is now, hopefully, in the process of looking specifically at that group who have daily records of the exact amount of 2,4-D that they use over 27 years. Since he has a good tumor registry -- my friends at

NIH tell me it is one of the best in the country -- he should be able to answer that question with some precision in this group who only use 2,4-D. They are not even using paraquat yet.

They should, looking at this group, might be able to answer that specific question, does 2,4-D do it. If, in fact, the answer to that is no, then one has to go back and ask about the other study which they did, then, what was it in that other study that, in fact, caused that non-Hodgkin's lymphoma.

I might just say I don't think there is any question at all about the non-Hodgkin's lymphoma. All those things were independently pathology verified, and I think that data is pretty good. It goes with a lot of data that Cantor has and other people, saying there does seem to be a lot of non-Hodgkin's lymphoma in farmers for some reason or other.

And so if we could answer that question, then I think that would point us in the right direction for asking the question why do farmers have non-Hodgkin's lymphoma and why do those guys in Sweden have the soft tissue sarcoma. Those are important kind of questions and maybe we can get pointed in that direction.

DR. BOND: I think the hypothesis of nitrates in drinking water, that has been offered most recently, is an intriguing alternative explanation for non-Hodgkin's lymphoma in farmers. As far as explaining the soft tissue sarcoma in Swedish studies, I think that is a methodologic problem with those studies. I don't think it has to do with any underlying biology.

In fact, the data that are available suggest that agricultural workers, forestry workers in Sweden are not at increased risk of connective tissue or soft tissue cancers.

DR. DOULL: The nitrates in water, that relates also to the nitrates that are put in this 2,4-D to inhibit rust, are you making that connection?

DR. BOND: No, I am talking about nitrates from fertilizer. I think NCI is exploring that hypothesis in the Nebraska study, looking at it. There is certainly an animal model for that type of association, but there is no animal model for 2,4-D causing non-Hodgkin's lymphoma.

DR. BURMEISTER: The combination of some of the herbicides, that are nitrosamines or something of that nature, interacting with the nitrates from the heavy nitrogen fertilizer in our part of the country, including Nebraska, is an

intriguing hypothesis.

DR. DOULL: With the triazines also.

DR. BURMEISTER: Well, I am not a toxicologist. I just am relating what people have told me, that there is that possibility apparently.

I think -- one thing that kind of continues along this line in terms of the non-Hodgkin's lymphoma being shown in a lot of studies to be elevated in the farmers, relative to the NCI study in Kansas, I have seen some criticism of that study because the Hodgkin's disease and the soft tissue sarcoma were both not statistically elevated.

To me, I think that is a good point instead of a negative point, because of what we know through the literature at least about only of those three, that predominantly NHL is the one that is suspected to be a problem in farmers, so the fact that only that of the three cancer types was shown in Kansas to be of importance, or whatever you want to call it, is a positive point the way I look at things. I wonder whether Dr. Bond would comment on his feelings on that.

DR. BOND: My only objection to that is that the author's conclusion was that their data supported the Hardell findings, and to find only one of the three apriori cancer

sites of interest related to herbicide use, to me, did not seem to lend support to a conclusion that there was corroboration between the studies.

DR. KILGORE: Dr. Swenberg had a question, but I want to make a comment before that. I want to compliment you on how smoothly you worked in those slides.

(Laughter.)

DR. BOND: I will take that as a compliment.

DR. SWENBERG: I would like to get a little bit of dialogue going between the two groups, because in your letter to us, you put things forth as their statement and your comments, and also in your introduction.

The first area that I would like to discuss is exposure. Can you tell me -- I would like to find out why the groups differ here on whether we have general population exposure or not, and they say the compound is sold in the garden stores. Tell me what is your reason for saying we don't have widespread exposure, and then we will ask the EPA if they agree.

DR. SERRONE: Well, we feel that based on our review of the literature that we have done, that basically, in the WHO report, that we feel there is very limited exposure outside

of an occupational work force to that 2,4-D. We do feel that that is a bone of contention between us, and we feel that our review of the data indicates that it is minimal exposure.

DR. SWENBERG: How do you define exposure? Is this a certain number of days per year, or just exposure, period?

DR. SERRONE: Well, there are some calculations that show that the exposure in outside populations is -- someplace here I have a note on that -- that the general population is less than .002 milligram per kilogram body weight per day is the figure that we have come up with in a review of the literature.

We feel that applicator crews absorb less than .1 milligram of 2,4-D per kilogram per day.

DR. SWENBERG: Is that per day of use for the homeowners?

DR. SERRONE: No, that is per day on an average basis over the year.

DR. SWENBERG: How many days do they use it?

DR. SERRONE: I wouldn't want to quote that off the top of my head right now.

DR. SWENBERG: Two? Three?

DR. EISENBRANDT: I don't think there are data

available on what a homeowner might not be exposed to. All the literature that is available talks more about the applicators, and for instance, that figure on .002 milligrams per kilogram per day of exposure, that is based on the population in an area where 2,4-D might be used.

The World Health Organization goes on to say that as far as the general population is concerned, any exposure is below detectable limits, and those are the data that were available.

DR. SWENBERG: And there is no reason to think those data have changed since '84 or whenever that was?

DR. EISENBRANDT: Not that I am aware of. I think possibly it depends on how the EPA defines their term. They use the term "high population" exposure. I am not quite sure what they meant. It could mean lots of people or high numbers.

DR. SWENBERG: Maybe we can get them to tell us.

DR. KILGORE: Quite correct. Jerry Blondell?

MR. BLONDELL: It was the high numbers of the population that are exposed. 2,4-D is probably one of the -- has been one of the number one herbicides sold for home use, and certainly the lawn care services also for many years were using 2,4-D more than other chemicals. So when we used

the term "high population" exposure, we are talking about a large number of people being exposed, not high levels.

DR. SWENBERG: Yours is based on large number regardless of what the exposure amount is in milligrams?

MR. BLONDELL: Right.

DR. SWENBERG: So it is probably a large number, but very low annual exposure, a couple of days a year.

MR. BLONDELL: Correct.

DR. SWENBERG: The other point that I wanted to delve into a bit was on the pharmacokinetic data.

In your opening remarks, you said that the pharmacokinetic data for the rat and the mouse were very similar, and yet when I read through the Canadian review, for instance, I came up with a half-time of the first phase in the rat of 1 hour and in the mouse of .013 hours. Those are vastly different.

DR. SERRONE: The half-life differences, that you are referring to are different, but what we are talking about is the general flow of the curve of the excretion in the urine and fraction of puddle dose, as well as that in the plasma showing the break point in those at approximately 50 milligrams per kilogram done at dose level.

DR. SWENBERG: But it is retained much longer in the rat than in the mouse?

DR. SERRONE: Yes.

DR. SWENBERG: One hundred times longer?

DR. SERRONE: Yes. There was a big difference in size between the rats and the mice, too, which probably accounts for a great deal of that, yes.

DR. KILGORE: Any other questions from the panel? Joe?

DR. GRISHAM: I would like to come back to the Hazeman paper and the issue of false positive Type 1 errors and get some further comments from the Agency people regarding this.

I usually leave statistical questions to Dr. Swenberg since he has so much fun with them. But it seems to me that this is certainly an issue of some profundity, and since this issue has been brought up by some in the federal establishment, and we always seem to be belabored by statistical aspects of data here, I wonder what your comments are about this is.

The fact that there can be on the basis of p less than .05 data, 50 percent Type 1 error, and with the trend test even higher, I wonder --

DR. VAN GEMERT: I would like to refer this question to our statistician in toxicology, Mr. Richard Levy.

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MR. LEVY: My name is Richard Levy. I am the leader of the biostatistics team, Tox Branch, EPA.

In regards to the question on Type 1 error, first, I would like to discuss the trend test Type 1 error and then the (Pere West) comparison Type 1 error.

Since we have referred to Hazeman several times this morning, I would like to once again quote from his paper.

"Although the concurrent control group is the most appropriate control group for decisionmaking, the use of historical control information can aid in the overall evaluation of the data. Rare tumors may require somewhat less stringent statistical evidence in a given study if the lowest spontaneous rate of the tumor can be demonstrated for historical control data."

The Cochran-Armitage statistic false positive rate is a function of both the tumor background rate and the experimental design. Using the (mod col) assimilation with 10,000 realizations of 2,4-D experimental design and the background rate estimated as low as .4 percent and as high as 4 percent, at the nominal .01 test level, the false

positive rate never exceeds .0181. For this trend, we note that the statistical significance is at .0005. I believe we have a significant trend and it is not chance variation.

In addition, I would like to comment before I go on to the Fischer exact test, that we have not considered Type 2 error. From the Pearce-Theron '77 paper, we see, assuming a fivefold increase for one dose experiment, at a .04 background, we could have as much as 20 percent Type 2 error.

From Hazeman's paper, once again the '84 paper, his table, discussed actual significant levels for Fischer's exact test is a function of spontaneous tumor frequencies. With a 4 percent background, which is the upper limit of what we have been discussing today, and would not be recommended by Hazeman according to his -- or any of the federal agencies according to the discussions on use of historical control data, the range of historical control data, since -- the range is sample size dependent. Sample size dependent tends to broaden as more studies are completed.

However, we will use the less conservative estimate of 4 percent and come up with at a nominal significance level of .05. The true Type 1 error associated with it would be .007. Thus, once again, with a .054 and a relatively

uncommon tumor, we feel that we are nearly significant. Hazeman recommends once again that while Type 1 significant tests should be -- in the NCI studies -- should be at .01 for common tumors, for uncommon rare tumors he suggests .05, so we are closing in on the .05.

I would like to comment further that the likelihood of observing six or more tumors of this type, in this experiment, is less than .031. With a background of 4 percent, with a background of 3 percent, it is .009, with a background of 2 percent, it is less than 10^{-4} , and as the background decreases toward .04, we approach a lot less than 10^{-5} likelihood of observing six or more of these tumors.

DR. GRISHAM: I would like to ask Dr. Koestner a question. Do you consider astrocytomas to be a rare tumor in adult or age two-year-old Fischer-344 rat?

DR. KOESTNER: As I say, in their study they excluded all tumors which were not diagnosed as astrocytomas. Now even if they include or that they have to include the tumors which are gliomas, which might be astrocytomas, but they were not specified as such, what else can they be if there is no other tumor. I think it is an astrocytoma or an undifferentiated astrocytoma, and the oligodendrogliomas

which immediately increases the level from which they started.

Now, that approaches close to 1 percent, but as I wanted to make a point, that with the seven sections we are going beyond that, because we can slowly approach that at 120 weeks or whatever, but there is then 2.9 percent, so it doesn't become a rare tumor anymore, and I don't think it is a rare tumor, even so it is not detected at that particular time.

Also, when one uses statistics to see what is the chances that there are five tumors here, I cannot really buy that, because the variation is so great, that whether there are five or four or so, this is irrelevant. We see in every experiment that there are more tumors than there should be in one group, and fewer tumors than there should be in another. So it really doesn't tell us a whole lot.

So, statistics alone just can't resolve that problem. I think this is what I want to say. It is a biological phenomenon, and not a statistical.

DR. KILGORE: Dr. Clarkson?

DR. CLARKSON: My question is on a slightly different line --

DR. SWENBERG: Let me just make a comment related

to that. Brain tumors have been called rare tumors in the past, but as we look and do a better job of the pathology, they are clearly increasing. So if you look at the historic controls from 10 years ago versus those from the last 3 years, you will see that there has been a distinct increase. We don't know what the reason for this is. Part of it is better ability to diagnose it and better knowing where they arise and looking in those areas.

Using the Solleveld paper and the historic two-year data, which we must remember has only three sections per brain, you come up with total brain tumors of .8. I think that was Bert's point. Hazeman has used 1 percent as his cutoff for calling it rare versus non-rare. So we are very close to that borderline. I think that one would be hard-pressed to make a strong argument that it is rare or that it is not rare. It is right at that level of where we are making that cutoff, so I just raise that for information.

DR. KILGORE: Tom?

DR. CLARKSON: I would like to ask the EPA group a general question. In your discussions and evaluation of the potential oncological effects of this compound, did you have a discussion on the possible mechanisms whereby 2,4-D

might produce cancer? That is, the Canadian report -- I keep referring to this; I have read the others, too -- they do call it, for example, in terms of the metabolism of this compound, that it doesn't appear to be terribly active as far as forming active intermediates, DNA adducts, and so forth, that, in fact, it is excreted unchanged, or excreted as a taurine or glycine conjugate, and so forth, and that it may possibly, for example, be a promotor, that is, it promotes plant growth, and so forth.

If this is so, I have some difficulties. We have already discussed at length the epidemiology. I have some difficulties trying to understand that if we were to believe the epidemiology, that is, that a person could be only exposed for two weeks and then develop this soft tissue sarcoma 26 years later, I have some difficulty understanding this.

If it was an aflatoxin type that formed some irreversible effects on DNA and then down the line you get cancer -- so, did you discuss the mechanisms at all?

DR. VAN GEMERT: No, we didn't discuss the mechanisms, but in terms of the animal studies, 2,4-D does not readily cross the blood brain barrier in low doses, but in high doses you do see a breakdown of the blood brain barrier,

so you would, at higher doses, probably see some in the brain.

As far as the soft tissue sarcoma, I wouldn't speculate on that.

DR. CLARKSON: What I am talking about is not only that it maybe gets there eventually, but it doesn't seem to be an active compound in forming DNA adducts --

DR. VAN GEMERT: I agree.

DR. CLARKSON: -- or producing irreversible effects of one form or another, that what I have seen of the pathology -- and with two distinguished pathologists here, I say this with great trepidation -- but the effects seem to be on things like the thyroid or pituitary, and so forth. If anything, it has some type of promotional effect.

If that were true, would you consider that these effects at high doses could be almost threshold type effects, that if it is not producing these tissue effects at lower levels, if it is not acting as a direct acting carcinogen, one wonders, therefore, what this would mean to humans at very, very low doses to which they are exposed, that is, to go in the face of (tack) and not say we are going to do a linear extrapolation here.

DR. VAN GEMERT: I don't think I care to speculate.

DR. CLARKSON: You should have a slide.

(Laughter.)

DR. KILGORE: Any other comments from the panel?

DR. MORGAN: I have a comment, Mr. Chairman, if I can make it at this point in time, if I can recover my spot here.

DR. KILGORE: Please do.

MR. MORGAN: Robert Morgan. I am Chairman of the Technical Committee of the Industry Task Force on 2,4-D Research Data.

This is directed basically to John Doull, who brought up a question, I guess, that I thought needed clarification concerning the nature of the test material used in our chronic studies.

John, I think as you well know, the EPA requires that the technical grade active ingredient be used in those studies, not pure active ingredient, and it was so used in our studies. In fact, it was a composite sample representing the material that was being produced by the member companies at that time. It is not a formulation, it is the technical grade acid as produced.

DR. DOULL: There is no question you did it as

required and as needed, but I guess my concern would be what would have been the technical material 30 years ago, when some of these epidemiology things were beginning to occur as compared to the technical grade today. I guess we have no real way of kind of getting a handle on that.

MR. MORGAN: That would be very difficult, I think. Perhaps it could be done in some isolated cases, but not in a general sense.

DR. DOULL: I have three little quickie things.

You are saying it doesn't get to the brain. Well, I thought it did get to the brain well.

DR. VAN GEMERT: It doesn't readily cross the blood brain barrier except at higher doses, and it does get into the brain at higher doses, yes; low doses, no.

DR. EISENBRANDT: I was just going to add some numbers to that. The amount normally present in the brain is only about 5 percent that is in the plasma, and the kind of doses required to cause an effect on the blood brain barrier, that is shown in the literature, is above 100 milligrams per kilogram dose before there is any effect on the blood brain barrier.

DR. DOULL: I guess I am trying to think of the

clinical history with suicides with 2,4-D and all that in terms of brain effects, and my impression was that I guess at suicide, that is a higher dose, so maybe that is why there is some literature saying it does get to the brain in that case.

A second small point. The EPA is consistently misspelling Fred Holmes name. It is H-o-l-m-e-s. As a Kansan, it is my obligation to point that out, that you must not misspell his name.

Third, there is a comment in here -- and you made that again, Dr. Bond -- Brian McMahon in here makes a strong statement about the fact that a single study doesn't make the link. That bothers me a little, because I think one really first-class study could do it. Isn't that really true?

DR. BURMEISTER: Traditionally, I would agree with Dr. McMahon's comment, that we always look at more than one study just because of the difficulties that we have talked about abundantly today, that are associated with epidemiological studies. Now, yes, I would think it would stand up if, indeed, there were really a very strong, very supportable epidemiological study. I suppose the point really is has such a study existed particularly relative to 2,4-D; probably not. That is the basis for what he is saying, I would think. Of course,

that is my opinion.

DR. DOULL: You know, we have cardinal rules in Tox, and I wondered if that was a cardinal rule in Epidemiology.

DR. BURMEISTER: Pretty close.

DR. DOULL: Pretty close. Okay.

DR. BOND: I think it is axiomatic among epidemiologists that a single study -- unless you have got the unique situation like we had with vinyl chloride, where you were seeing angiosarcomas in the animals, and then angiosarcoma cases started to appear in the humans. A single study in that case, I think was sufficient to conclude that there was a human effect. But we are not even approaching that at all with 2,4-D.

With most epidemiological studies, it is unusual to have that kind of effect.

DR. KILGORE: Dr. Swenberg has an additional question of EPA, I believe.

DR. SWENBERG: No. We have the luxury this morning of having enough time to thoroughly discuss something, and it is very nice. But I would like to discuss kind of the bottom line here, that is, the categorization of this data. Now, the

EPA came up with an Interim Group C as their recommended classification. The Industry Group has come up with up a Group E, evidence of noncarcinogenicity. Yet, everything we have kind of heard is that the human evidence is inadequate and that the animal evidence is inadequate. It is difficult to prove a negative, I agree with that, and everybody seems to be fairly comfortable with there are some problems in the positivity of both the animal data sets and the animal sets.

If I look at Table I from the Federal Register, we have a category for that. If you look at inadequate human and inadequate animal, that is a Category D. I guess I would ask for the response from both groups as to why they believe that this should not be a Group D carcinogen.

DR. KILGORE: Why don't we start with EPA.

DR. VAN GEMERT: We feel that the evidence in the rat study is equivocal, that that is tantamount to limited evidence. So we chose Category C because the tumor response was marginally statistically significant in a study having an inadequate design, which would fall into Group C.

The definition of "limited" in the Federal Register was that the data suggest a carcinogenic effect, but are limited because of several parameters. The studies involved

a single species strain or experiment that do not meet the criteria for sufficient evidence, or -- that's not it -- the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up or poor survival, too few animals, or inadequate reporting.

DR. SWENBERG: And you are going on inadequate dosage, is that correct?

DR. VAN GEMERT: That is correct.

DR. DOULL: That it wasn't MTD?

DR. VAN GEMERT: That is true.

DR. SWENBERG: But on the new MTD guidelines, where it is a predicted dose, I think this study would be accepted as meeting the MTD, isn't that correct?

DR. VAN GEMERT: The problem with that pharmacokinetic study was that it was a single bolus dose rather than, say, in this sort of study, repeated exposure over a long period of time, where you do get some modification of the metabolic change. So there are some flaws with the pharmacokinetic study.

DR. SWENBERG: But the interpretation of whether or not this is reasonably close to an MTD to accept the data,

that is fairly tenuous, isn't that correct? I mean this is not an overwhelming case of underdosage; this would be a matter of very fine tuning, isn't that correct? You certainly would not recommend doubling the dose.

DR. VAN GEMERT: No.

DR. SWENBERG: So we are within what was acceptable in those guidelines, isn't that correct? So then it doesn't become limited. I mean that knocks out limited. So that is why I think it ends up as a D.

Do you have a response to that?

DR. VAN GEMERT: No.

DR. SWENBERG: Okay. I turn it to the industry then. What is their feeling as to why this should not be called a Category D?

MR. MORGAN: I will try to respond to that. I think our point was made that we didn't feel that the findings in the rat study were equivocal; therefore, there were no findings of an oncogenic effect, which would clearly put us into an E category, although we did not state that to be our position with certainty. We just pointed out we didn't believe it to be an oncogen.

DR. DOULL: How about the other half of that, the

epidemiology?

DR. BOND: If I could respond to that. I found myself in the predicament, Mr. Blondell was in, in that the categories are really insufficient for judging epidemiology evidence.

DR. DOULL: Inadequate.

(Laughter.)

DR. BOND: No. I think with 2,4-D we happen to be in a situation where there have been multiple studies done, and I wouldn't classify the total package as being inadequate. I think there is quite a bit of work there.

As I tried to demonstrate in my slides, and maybe successfully and maybe not successfully, my interpretation is that we can rule out fairly modest increased risks of non-Hodgkin's lymphoma and soft tissue sarcoma related to 2,4-D based on the epidemiology.

Unfortunately, there is no category that allows you to say that. The categories almost imply that you can rule out any effect, and I don't think on the basis of any toxicology study, or any epidemiology study, you are ever going to be in a position of ruling out any effect.

I mean you get the best evidence that is available

and you make a decision. There is no quantitative room in those categories for assessing the strength of association. My feeling is that we can rule out strong associations, we can rule out modest associations. We probably will never have enough data to rule out very weak associations.

DR. SWENBERG: Well, it seems to me that if the compound gets categorized as a C, then it is labeled for life. If it gets categorized an E, then there is no more work done on it and we never resolve this issue. But if it's a D, we have got epi studies that are coming out yet, we have got the potential of hypothesis testing, animal studies, and the door is still open. We haven't labeled the compound, we haven't said that it is safe from hereon out for the human population.

That seems reasonable to me on scientific grounds. I would like to hear arguments against it.

MR. ENGLER: My name is Engler from the Toxicology Branch. Maybe I would like to add some words to why we still feel that probably C might be the correct classification, because we agree with you, Dr. Swenberg, that the studies are, in fact, fairly well conducted. They are not inadequate studies. They are very adequate studies.

About the MTD, I think you are probably right, I

think that is close. It's a very close call.

So, therefore, we believe that the tumors, the brain tumors we are seeing is, in fact, limited evidence, and that would put it, in our classification, into a C. It is not inadequate data which would put it in a D.

DR. GRISHAM: It is not inadequate data, but it is inadequate evidence. We are not arguing about the data; we are arguing about the evidence.

DR. DOULL: Exactly.

MR. ENGLER: Well, we feel it is limited rather than inadequate.

DR. KILGORE: Any other comments from the panel?

DR. KOESTNER: I just want to respond. I did study the EPA response very well, and I think they made too much evidence, really, on the statistics. This is my criticism, and from the statistical standpoint, then they fail to list that limited evidence. One has to really consider the biological data. With their statistics, the comparison was wrong, really, because they did not include all these tumors from the historical data, and this is very clearly spelled out here on page 4 of their report.

DR. SWENBERG: We really only have one control group

that you can have statistics on that --

DR. KOESTNER: I understand that.

DR. SWENBERG: -- and that is the control of this study, because you did seven sections. We have no other data base that we can use.

DR. KOESTNER: I understand that.

DR. KILGORE: Any other comments from the panel?

(No response.)

DR. KILGORE: I will call for any comments from the floor. Are there any comments anyone wishes to make?

(No response.)

DR. KILGORE: If not, then we will adjourn to 1:15. I hope that we will have the reports available to you early this afternoon.

(Luncheon recess taken at 11:10 a.m.)

AFTERNOON SESSION

(1:15 p.m.)

DR. KILGORE: I would like to reconvene the SAP panel meeting.

First of all, I would like to issue a report on our conclusion on 2,4-D.

The SAP does not agree with the Peer Review Committee's conclusion that the available 2,4-D oncogenicity data should be classified as an Interim Category C, Possible Human Carcinogen.

The panel believes that the rat and mouse oncogenicity studies were adequate in design and conduct. The data were negative for oncogenicity in female rats and both sexes of mice. The increased incidence of astrocytomas in male rats exposed to 45 milligrams per kilogram 2,4-D was considered equivocal evidence of oncogenicity.

The panel believes that additional testing is required to resolve this issue. This testing should specifically address the astrocytoma issue by repeating an oncogenicity study. The study design should include two male rat control groups of 50 each and two female groups of the same size, exposed to 45 milligrams per kilogram of 2,4-D -- excuse



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